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EXAMINER

HAMA, JOANNE

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/803,095

Applicant(s)

MESAELI, NASRIN

Examiner

Joanne Hama, Ph.D.

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 March 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 6-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 3/18/04, 6/14/04 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

This Application, filed March 18, 2004, claims priority to U.S. Provisional Application, 60/455,399, filed March 18, 2003.

Claims 1-11 are pending.

### ***Election/Restrictions***

Applicant's election without traverse of Group I, claims 1-5, in the reply filed on March 3, 2005, is acknowledged.

Claims 6-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 3, 2005.

Claims 1-5, drawn to a transgenic mouse comprising a transgenic construct comprising a nucleic acid sequence encoding calreticulin (CRT) operably linked to a promoter, wherein expression of exogenous CRT in vascular smooth muscle cells results in hemangioma formation, is under consideration.

### ***Information Disclosure Statement***

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate

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paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Pages 28-39 of the specification comprise a listing of references. The Examiner has not considered these references. References to be considered must be indicated on an IDS and copies of references must be submitted.

### ***Specification***

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Two nucleotide sequences described on page 5, lines 23-25, of the specification have no SEQ ID NOs.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a SM22 $\alpha$  promoter,

2) a transgenic mouse comprising a nucleic acid sequence encoding mouse calreticulin (CRT) operably linked to SM22 $\alpha$  promoter comprising 445 bases upstream of the start site, wherein the transgenic mouse exhibits hemangioma formation, and

3) a method of making a transgenic mouse comprising a nucleic acid sequence encoding mouse calreticulin (CRT) operably linked to SM22 $\alpha$  promoter comprising 445 bases upstream of the start site, wherein the transgenic mouse exhibits hemangioma formation,

does not reasonably provide enablement for:

1) a transgenic mouse comprising a nucleic acid sequence encoding any species of calreticulin operably linked to any promoter and

2) a method of making a transgenic mouse comprising a nucleic acid sequence encoding any species of calreticulin operably linked to any promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

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nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is to a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a promoter, a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a promoter, wherein expression of calreticulin is expressed in vascular smooth muscle wherein said transgenic mouse exhibits hemangioma formation and to a method of making said mouse.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention broadly encompasses the use of any promoter in the method of making a transgenic mouse wherein the transgene construct is comprised of a nucleic acid sequence encoding CRT operably linked to any promoter (in particular, see claim 4). The specification, at the time of filing, teaches that a transgenic mouse comprising a transgene construct comprising nucleic acid sequence encoding mouse CRT, tagged with an HA epitope tag, operably linked to a mouse SM22 $\alpha$  promoter comprising 445 base pairs upstream of the start site, resulted in mice that exhibited hemangioma (specification, page 16 to 17, under "SMCRT transgenic mice"). While the specification provides this teaching, the specification does not teach how to enable an artisan the full breadth of any promoter in the claimed invention. The art at the time of filing teaches that the identification of any promoter was unpredictable. For example, Goswami et al. (2003, Journal of Molecular Evolution, 57:44-51) teach some of the analyses used to characterize a promoter. Goswami et al. show by 5' deletion analysis that BD2, a greater 5' deletion of the TGF- $\beta$ 5 promoter than BD3, has more activity than BD3, suggesting that the 5' deletion in BD2 uncovered a negative regulator in the promoter (page 46, column 2, first paragraph, lines 3-7). Goswami et al. also show that while there is this difference in promoter activity between the two constructs transfected in XTC cells (*Xenopus* tadpole cell line), there is no difference in the activity of the promoters when transfected in A6 cells (*Xenopus* adult kidney fibroblast cell line). This result suggests that there is a difference in the transcriptional factors between the cell

types (page 46, column 2, first paragraph, lines 7-10). Goswami et al. also show that there is a difference in promoter regulation, depending what animal species that promoter is from and into which cells the reporter construct is transfected. TGF- $\beta$ 5, which is found in rats and frogs, was found to be regulated differently. *Xenopus* TGF $\beta$ -5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activities of TGF $\beta$ 1 and TGF- $\beta$ 5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4). As illustrated by Goswami, selecting a regulatory region of a gene as a promoter is not intuitive and requires extensive characterization. This is undue experimentation. One skilled in the art cannot define a regulatory region of a gene as a promoter and expect that another skilled in the art would select the same sequence without guidance.

In addition to the teachings of Goswami, the art also teaches that an artisan cannot predict whether a tissue specific promoter from one species of animal will necessarily work in another species of animal. For example, Cowan et al., (2003, *Xenotransplantation*, 10: 223-231) teach promoters of three human genes, ICAM-2, HCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve

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species-specific gene expression in pigs (Cowan, et al., page 223, 1<sup>st</sup> parag.). Thus, in view of the unpredictability of promoter in the art of transgenesis, the working example provided in the specification does not allow a skilled artisan to obtain any tissue specific promoter from any animal.

The claims broadly encompass any SM22 $\alpha$  promoter. This encompasses any part of the upstream regulatory region of a gene. The specification at the time of filing teaches that a promoter comprising 445 bases upstream of the start site was used in the instant invention (specification, page 16). However, the art teaches that not all regulatory regions upstream of the start site have transcriptional activity. For example, Li et al. (1996, Journal of Cell Biology, 132: 849-859) teaches the relative transcriptional activity of isolated SM22 $\alpha$  promoters. In addition to demonstrating that some SM22 $\alpha$  promoters have transcriptional activity when transfected into cultured cells (pMS2735-luc, pSM1343-luc, pSM-445) (Li et al., page 851 under "Identification of the SM22a 5' Flanking Region That Confers the Transcriptional Activity In Vitro," see also Figure 2). Li et al. also teach an SM22 $\alpha$  promoter (pSM144-luc) that had low transcriptional activity. Thus, a skilled artisan would need to be taught the parameters of what was used as a promoter. A "promoter" is a functional term, but there are no parameters associated with it when one skilled artisan says that one was isolated. One skilled artisan could tell another skilled artisan that a keratin promoter was used to express a gene of interest in skin. However, another skilled artisan could isolate the same promoter, but it could be 1kb larger than the first skilled artisan's promoter. The two artisans have promoters that express in skin, but one promoter could have more robust

expression than the other promoter. It could be possible that the robust expression is what is vital for a skilled artisan to see a phenotype in a transgenic animal. Thus, as taught by Li et al., the claimed invention is not enabled for the full scope of any SM22 $\alpha$  promoter.

The claims, as filed, broadly encompass transgenic mice comprised of a transgene comprised of a nucleic acid sequence encoding CRT obtained from any species of animal (see in particular, claims 1, 3, 4). The specification, at the time of filing, teaches that SMCRT transgenic mice were comprised of a nucleic acid sequence encoding mouse CRT and HA epitope (specification, page 17). However, the art teaches that an artisan cannot predict that a protein from one species of animal will necessarily function in another species of animal. For example, work by Hammer et al., (1990, Cell: 63: 1099-1112) teach that transgenic mice that overexpressed human HLA-B27 and human  $\beta$ 2-microglobulin (h $\beta$ 2m) did not develop the human disease, spondyloarthropathies, whereas a rat that overexpressed human HLA-B27 and human  $\beta$ 2-microglobulin (h $\beta$ 2m) did (page 1099, second column, second paragraph). In this example, despite expressing the same human genes, the transgenic mouse and rat had different phenotypes. For this reason, a skilled artisan cannot predictably determine whether a nucleic acid sequence of a protein obtained from one species of animal will necessarily function in another species of animal. In order for an artisan to determine if one nucleic acid sequence would encode a protein that was active in another species of animal would need to be empirically determined. This is undue experimentation, as no guidance was given as to how an artisan would consider certain characteristics of one

protein from one species of animal over another.

Thus, the specification, while being enabling for:

1) a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a SM22 $\alpha$  promoter,

2) a transgenic mouse comprising a nucleic acid sequence encoding mouse calreticulin (CRT) operably linked to SM22 $\alpha$  promoter comprising 445 bases upstream of the start site, wherein the transgenic mouse exhibits hemangioma formation, and

3) a method of making a transgenic mouse comprising a nucleic acid sequence encoding mouse calreticulin (CRT) operably linked to SM22 $\alpha$  promoter comprising 445 bases upstream of the start site, wherein the transgenic mouse exhibits hemangioma formation,

does not reasonably provide enablement for:

1) a transgenic mouse comprising a nucleic acid sequence encoding any species of calreticulin operably linked to any promoter and

2) a method of making a transgenic mouse comprising a nucleic acid sequence encoding any species of calreticulin operably linked to any promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at <http://www.uspto.gov/web/menu/current.html#register>).

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

While the specification and the art provides adequate written description for the isolated nucleic acid sequence of SM22 $\alpha$ -CRT as SEQ ID NO. 1 and SM22 $\alpha$ -CRT-HA as SEQ ID NO. 2 the specification fails to adequately describe other nucleic acid sequences which hybridize to these sequences that do not encode these proteins. The

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claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, while the Applicant has described the SM22 $\alpha$  promoter and the mouse CRT cDNA that was used in the instant invention, the Applicant has not described structure and function for fragments or variants of SM22 $\alpha$  promoter and the structure and function of different species of CRT in a transgenic mouse, such that an artisan would be able to identify any functional SM22 $\alpha$  promoter and any CRT protein such that both would be functional in a transgenic mouse. While the art may teach in great detail the many parameters one can change in hybridization conditions to obtain a nucleic acid sequence by altering the temperature, salt concentrations, time of incubation, length of nucleic acid and composition of the nucleic acid composition, the specification and the art fail to describe the relevant identifying characteristics such that an artisan could obtain any SM22 $\alpha$  promoter and any CRT which would function in a transgenic mouse. The skilled artisan cannot envision all the possible variant nucleic acid sequences which would hybridize but do not encode a CRT protein, nor can a skilled artisan envision all possible sequences of a SM22 $\alpha$  promoter that would direct expression of CRT in vascular

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smooth muscle cells, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the nucleic acid sequence encoding mouse CRT operably linked to the disclosed SM22 $\alpha$  promoter (SEQ ID NO. 1) and the nucleic acid sequence encoding mouse CRT and an HA epitope operably linked to the disclosed SM22 $\alpha$  promoter (SEQ ID NO. 2) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (2001, J. of Clinical Investigation, 107:1245-1253).

Claim 4 is to a method for producing a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding calreticulin and a transcriptional control region, wherein the control region comprises a promoter.

Nakamura et al. teach how to make a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a cardiac alpha-myosin heavy ( $\alpha$ -MHC) promoter (Nakamura, et al., page 1246, 1<sup>st</sup> col., 1<sup>st</sup> parag.).

The claim, as filed broadly encompasses any promoter. Thus, the teachings of Nakamura et al. anticipate claim 4.

It is noted that Nakamura et al. anticipates claim 1 because while Nakamura et al. teach transgenic mice comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a  $\alpha$ -MHC promoter, the art teaches that while calreticulin is associated with the endoplasmic reticulum (Dai, et al., page 2359, 2<sup>nd</sup> col., 2<sup>nd</sup> parag.) calreticulin is found in extracellular locations (Dai, et al., page 2359, 2<sup>nd</sup> col., 3<sup>rd</sup> parag.). Dai et al. teach that "an exciting finding is that calreticulin has been reported to play a role in both the thrombotic and inflammatory responses of circulating blood (Dai et al., page 2359, 2<sup>nd</sup> col., 3<sup>rd</sup> parag., lines 2-4). Thus, because the art teaches that calreticulin is in the circulatory system, it would be expected that calreticulin would contact smooth muscle cells of blood vessels and cause

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hemangioma. While Nakamura et al. do not specifically teach that smooth muscle cells of transgenic mice comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a  $\alpha$ -MHC promoter exhibit hemangioma, an artisan would expect to find hemangioma in a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a  $\alpha$ -MHC promoter, based on the teachings of Dai et al. who teach that calreticulin is found in the circulatory system. Thus, Nakamura et al. anticipate claim 1.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dai et al. (1997, Arterioscler Thromb Vasc Biol, 17:2359-2368) in view of Li et al., (1996, Journal of Cell Biology, 132: 849-859).

Claim 3 is directed to a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a SM22 $\alpha$  promoter. Claim 5 is directed to a method according to claim 4 (a method for producing a transgenic mouse comprising a nucleic acid sequence encoding calreticulin operably linked to a promoter) wherein the promoter comprises a SM22 $\alpha$  promoter. Claim 1 is the independent claim.

Dai et al. teach that a rat model of intimal proliferation displayed inhibition of plaque formation in tissues treated with human or rabbit calreticulin (Dai et al., page 2363, 1<sup>st</sup> col., 2<sup>nd</sup> parag. under "Reduced Intimal Hyperplasia After Calreticulin Infusion at Sites of Balloon Injury," lines 7-11). While Dai et al teach treatment of arterial tissue with human or rabbit calreticulin protein, they do not teach an expression construct comprising a nucleic acid sequence encoding calreticulin operably linked to a vascular smooth-muscle promoter.

Li et al. teach that a SM22 $\alpha$  promoter comprising the first exon of SM22 $\alpha$  to – 2735 bp (could express a reporter transgene (luc) at a level similar to a promoter comprising –445 bp, as demonstrated in a transient transfection assay using primary rat aortic smooth muscle cells (SMCs) (Li et al. page 851, 1<sup>st</sup> col., 2<sup>nd</sup> parag., pages 5-11). Li et al. also teach that transgenic mice comprising a nucleic acid sequence encoding lacZ operably linked to the –2735 SM22 $\alpha$  promoter expressed in the descending aorta of an adult transgenic mouse (Li, et al., page 856, 1<sup>st</sup> col. under "Specific Expression of the SM22 $\alpha$  Promoter in Conductive Arterial, but not Venous SMCs, see also Figure 7B). Li et al. also teach that transgenic mice comprising a nucleic acid sequence encoding lacZ operably linked to the –445bp SM22 $\alpha$  promoter could also express in a similar temporospatial expression pattern as the –2735 SM22 $\alpha$  promoter (Li et al., page 856, 1<sup>st</sup> col., 1<sup>st</sup> parag. under "The 445 bp of 5'-Flanking Sequence Is Sufficient to Provide Temporospatial Expression Specificity of the SM22 $\alpha$  Promoter").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a transgene comprising nucleic acid

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sequence encoding rabbit, human, or mouse calreticulin operably linked to the -445 SM22 $\alpha$  promoter. It would have also been obvious to one having ordinary skill in the art to take the transgene and to use it in a method for producing a transgenic mouse whose genome comprises a transgene comprising a nucleic acid sequence encoding human rabbit, or mouse calreticulin operably linked to the -445 SM22 $\alpha$  promoter.

One having ordinary skill in the art would have been motivated make a transgene comprising nucleic acid sequence encoding rabbit or human calreticulin operably linked to either the -445 SM22 $\alpha$  promoter in order to obtain a calreticulin expression system that expresses in smooth muscle cells as Dai et al. teach that calreticulin protein has a therapeutic effect on rat arterial tissue. An artisan of ordinary skill could then use the transgene in *in vitro* studies on smooth muscle cells. One of ordinary skill in the art would also have been motivated to make a transgenic mouse comprising a transgene comprising nucleic acid sequence encoding rabbit or human calreticulin operably linked to either the -445 SM22 $\alpha$  or -2735 SM22 $\alpha$  promoter, in order to obtain a mouse that expresses calreticulin in smooth muscle and exhibits a phenotype of a reduction in intimal proliferation.

There would have been a reasonable expectation of success given the results of Dai et al. who teach that calreticulin has a therapeutic effect in rat arterial tissue and Li et al. who teach that the -445 SM22 $\alpha$  promoter expresses in arterial smooth muscle. Further, Li et al. teach transgenic mice comprising a transgene comprising a nucleic acid sequence encoding lacZ operably linked to the -445 SM22 $\alpha$  promoter, wherein the transgenic mice exhibit lacZ expression in arterial tissue. There would have been

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reasonable expectation of success to use the transgene comprising a nucleic acid sequence encoding calreticulin operably linked to the -445 SM22 $\alpha$  promoter in a method for making a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to either the -445 SM22 $\alpha$  promoter.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

### **Conclusion**

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

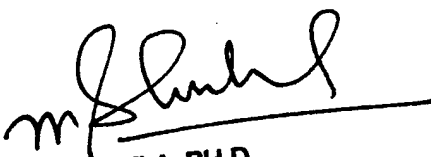
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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